The Oncologist®

Gastrointestinal Cancer

Association Between Tumor Progression Endpoints and Overall Survival in Patients with Advanced Neuroendocrine Tumors

Monica Ter-Minassian,[a,b,e] Sui Zhang,[a] Nichole V. Brooks,[a] Lauren K. Brais,[a] Jennifer A. Chan,[a] David C. Christiani,[b] Xihong Lin,[c] Sylvie Gabriel,[d] Jérôme Dinet,[d] Matthew H. Kulke[a]

[a]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [b]Department of Environmental Health and [c]Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA; [d]Ipsen Pharma, Boulogne-Billancourt, France; [e]Kaiser Permanente, Rockville, Maryland, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Neuroendocrine tumors • Somatostatin analogs • Progression-free survival • Overall survival • Landmark analysis

Abstract

Endpoints related to tumor progression are commonly used in clinical trials of novel therapeutic agents for neuroendocrine tumors (NETs). Whether improved tumor control translates into improved overall survival (OS), however, is uncertain. We assessed associations between tumor progression endpoints and OS in observational cohorts of patients with advanced neuroendocrine tumors treated with somatostatin analogs or with everolimus. We identified 440 patients with advanced NET who had received treatment with single-agent somatostatin analogs and 109 patients treated with everolimus, all of whom were treated at our institution and were evaluable for both tumor progression and survival. We assessed associations between progression-free survival (PFS) and OS by using the Kendall tau test, and we assessed associations between tumor progression and OS by using a landmark analysis. In the 440 patients treated with somatostatin analogs, we observed a significant correlation between PFS and OS by using the Kendall tau test (0.31; $p < .0001$). Additionally, the development of progressive disease was associated with OS in a landmark analysis, at landmark times of 6, 12, 18, and 24 months. In the 109 patients treated with everolimus, we similarly observed a significant correlation between PFS and OS by using the Kendall tau test (0.44; $p < .0001$) and associations between progressive disease and OS by using a landmark analysis at 3, 6, and 12 months. In these observational cohorts of patients with metastatic NET treated with single-agent somatostatin analogs or everolimus, longer times to disease progression and longer PFS were both associated with improved OS. Our findings support the continued use of disease progression endpoints in NET clinical trials. ***The Oncologist*** 2017;22:165–172

Implications for Practice: Clinical trials in patients with advanced neuroendocrine tumors have used progression-free survival as a primary endpoint. While there is a general assumption that slowing or halting tumor growth is beneficial, little direct evidence links improvements in progression endpoints to improvements in overall survival. This study assessed associations between tumor progression endpoints and overall survival in observational cohorts of patients with advanced neuroendocrine tumor treated with somatostatin analogs or everolimus. Longer times to disease progression and improved progression-free survival were both associated with improved overall survival. The findings support the continued use of tumor progression endpoints in clinical trials for neuroendocrine tumors.

Introduction

Although neuroendocrine tumors (NETs) may pursue a clinical course that is more indolent than that of other malignancies, they are almost always fatal in patients who develop advanced, unresectable disease [1, 2]. Several new systemic treatments to control tumor growth in patients with advanced NET have been evaluated in large, randomized studies and have gained widespread use in recent years [3–8]. These randomized studies have relied on time to tumor progression or progression-free survival (PFS) as a primary endpoint. In part because these studies used progression as a primary endpoint, the effect of new therapeutic agents on overall survival (OS) has been difficult to assess.

The use of PFS as a primary endpoint in clinical trials for advanced NETs was initially recommended in a report from the National Cancer Institute's Neuroendocrine Tumor Clinical Trials Planning Meeting in 2011 [9]. This recommendation was based in large part on feasibility considerations: in particular, a concern that the relatively long OS durations of patients with

Correspondence: Matthew Kulke, M.D., Dana-Farber Cancer Institute, D1220, 450 Brookline Avenue, Boston, MA 02215 USA. Telephone: 617 632 5136; e-mail: matthew_kulke@dfci.harvard.edu Received April 27, 2016; accepted for publication September 02, 2016; published Online First on February 8, 2017. http://dx.doi.org/10.1634/theoncologist.2016-0175

advanced neuroendocrine tumors would effectively preclude trials of novel agents from being performed using an OS endpoint. Since then, several novel therapies have been approved for use in patients with advanced NET based on their ability to slow tumor progression. The mammalian target of rapamycin (mTOR) inhibitor everolimus and the tyrosine kinase inhibitor sunitinib both improve PFS in pancreatic NET; everolimus was also recently confirmed to improve PFS in nonpancreatic NET [5, 8, 10]. Although these randomized studies clearly demonstrated improvements in PFS, they did not show clear improvements in OS, although the number of deaths in these studies was relatively low at the time of data analysis [4–6, 8]. Preliminary results of a recent randomized study of peptide-receptor radiotherapy in neuroendocrine tumors suggested a trend toward improved OS, although the number of events at the initial reported analysis was too small to permit definitive conclusions [11].

Recently, somatostatin analogs (SSAs), which previously were used primarily to treat symptoms of hormone hypersecretion, have been shown to also slow tumor growth. The antitumor effect of a long-acting formulation of octreotide (octreotide LAR) was evaluated in a study that randomly assigned patients with advanced small intestine neuroendocrine tumors to receive treatment with octreotide LAR 30 mg monthly or placebo [12]. Patients receiving octreotide LAR in this study experienced significantly longer time to tumor progression than those receiving placebo. No overall survival benefit was observed in patients receiving octreotide in the PROMID study, although the study was limited in size and the survival analysis was based on a total of only 85 patients [13]. In a more recent study, patients with a broad range of advanced gastroenteropancreatic neuroendocrine tumors were randomly assigned to receive treatment with the SSA lanreotide depot or placebo [3]. This study demonstrated significantly longer PFS in patients receiving lanreotide than in those receiving placebo, leading to U.S. Food and Drug Administration (FDA) approval for this indication. Mature overall survival data from this study are not yet available. In part because of their favorable toxicity profile, SSAs are now commonly used as a first-line treatment to control tumor growth in patients with advanced NET [14].

Although there is a general assumption that slowing or halting tumor growth is beneficial, relatively little direct evidence clearly links improvements in progression endpoints to improvements in OS in patients with advanced NET. The question of whether PFS improvements are related to improvements in OS is particularly relevant in the case of SSAs, which may be initiated relatively early in a patient's disease course, and which patients may continue to receive for many years. To further assess the extent to which progression endpoints might be associated with OS in patients with advanced neuroendocrine tumors, we investigated potential associations between disease progression, PFS, and OS in a large cohort of neuroendocrine patients treated with single-agent SSAs at our institution and in a smaller cohort of patients receiving treatment with everolimus.

Materials and Methods

Study Population

Patients were identified from an institutional database enrolling consecutive neuroendocrine tumor patients between 1995 and 2013. Patients provided informed consent for enrollment into the database at the time of their initial clinic visit. Consent rates for the study exceeded 95%. Of a total of 1,330 patients enrolled, we identified 440 with metastatic NET who had received treatment with single-agent SSA and were evaluable for tumor progression, based on medical record review. We identified a second cohort of 109 patients who had received treatment with everolimus and were also evaluable for progression and survival endpoints. Histologic diagnosis of neuroendocrine tumor was confirmed in the pathology department at Dana-Farber/Brigham and Women's Cancer Center. Medical information was abstracted from patient questionnaires and the medical record. The study was approved by the Dana-Farber Cancer Institute Institutional Review Board.

Statistical Analysis

For the purposes of this study, progression was defined as evidence of radiologic disease progression (based on clinical or radiology report; Response Evaluation Criteria In Solid Tumors [RECIST] progression was not required) or evidence of clinical progression as documented in the medical record. To further capture progression events that may not have been captured in the medical record, initiation of a new therapy was also considered a progression event. PFS was defined as time from the start of SSA treatment until progression or death, whichever event came first. Patients were censored for progression-free survival at the date of their last available follow-up visit. OS was defined as the time from SSA initiation to the date of death from any cause. Survival data were obtained from the medical record or, if not available, from the Social Security Death Index. Associations between PFS and OS were assessed by using the Kendall tau rank correlation and bootstrap validation [15]. Associations between the development of disease progression and OS were assessed by using a landmark analysis [16] comparing survival from the landmark time for patients who had progressed with that among patients who had not progressed at 6, 12, 18, and 24 months after initiation of treatment with an SSA at 3, 6, and 12 months after initiation of everolimus. Of note, in a landmark analysis, patients who die before the landmark time are excluded from the analysis to avoid confounding. Hazard ratios (HRs) were assessed with a Cox proportional hazards model adjusting for age, gender, tumor differentiation, and tumor origin and post-progression treatments (for OS). Kaplan-Meier estimates were used to calculate median OS durations for patients with progression versus those without progression at each landmark time. Subgroup analyses were performed on the basis of tumor origin, functional status (presence of symptoms of hormone hypersecretion), and elevations in the biomarker chromogranin A (CgA) (defined as two times the upper limit of normal). Differences in subgroups were assessed by using a test for interaction (cross-product or likelihood ratio test for more than two subgroups).

Results

Characteristics of Patients Receiving Treatment with SSAs

We identified a total of 440 patients with metastatic NETs who had received treatment with single-agent SSA and were evaluable for both progression and survival (Table 1). The median age was 57 years; most patients had well differentiated histology, and approximately half had primary bowel neuroendocrine

Table 1. Progression-free and overall survival for patients receiving somatostatin analogs

Variable	PFS			OS		
	Events (progression + deaths[a]) (*n/n*)/at risk, *n/n*	Median PFS (95% CL), yr	*p* value[b]	Events (deaths) (*n/n*)/at risk, *n/n*	Median OS (95% CL), yr	*p* value[c]
Entire cohort[d]	311/440	1.5 (1.2, 1.8)		215/440	6.4 (5.9, 8.0)	
Age						
≥55 yr	173/252	1.5 (1.2, 2.1)	.25	135/252	5.9 (4.8, 6.8)	<.0001
<55 yr	138/188	1.3 (1.0, 1.9)		80/188	8.2 (6.2, 11.5)	
Gender						
Male	151/206	1.2 (1.0, 1.5)	.02	110/206	5.8 (4.7, 6.3)	.42
Female	160/234	2.0 (1.4, 2.6)		105/234	8.2 (6.4, 10.7)	
Tumor origin						
Small bowel	145/224	2.2 (1.8, 2.9)		105/224	8.1 (6.2, 8.8)	
Pancreas	72/93	0.9 (0.6, 1.1)	<.0001	46/93	5.4 (4.1, 9.6)	.12
Other	94/123	1.2 (1.0, 1.6)	.0003	64/123	5.7 (4.2, 6.6)	.02
Tumor histology						
Well differentiated	300/427	1.5 (1.3, 1.9)	.01	207/427	6.7 (6.0, 8.2)	.03
Poorly differentiated	11/13	0.5 (0.3, 0.9)		8/13	4.1 (1.1, NE)	
Functional status						
Functional	146/204	1.4 (1.1, 1.9)	.36	98/204	6.2 (5.7, 8.0)	.54
Nonfunctional	165/236	1.5 (1.2, 2.1)		117/236	7.3 (5.7, 8.4)	
Baseline CgA						
<2 times ULN	114/181	2.1 (1.4, 2.8)		59/181	9.6 (7.4, 12.6)	
≥2 times ULN	172/206	1.2 (1.0, 1.5)	<.0001	126/206	5.4 (4.6, 6.0)	.0005
Missing	25/53	2.9 (0.7, NE)	.67	30/53	6.2 (3.6, 11.9)	.0002

[a]147 (47%) radiological progression, 137 (44%) next treatment, 3 (10%) clinical progression, and 24 (6%) deaths without any progression.
[b]Calculated with a Cox model adjusted for age, gender, tumor differentiation and tumor origin, CgA level, and functional status
[c]Calculated with Cox model adjusted for age, gender, tumor differentiation and tumor origin, CgA level, functional status, and postprogression treatments
[d]332 patients received octreotide and 8 patients received sequential octreotide and lanreotide.
Abbreviations: CgA, chromogranin A; CL, confidence limits; NE, not estimable; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

Table 2. Landmark analysis of associations between progressive disease and overall survival at 6, 12, 18, and 24 months (overall cohort) in patients receiving treatment with somatostatin analogs ($n = 440$)

Landmark time (mo)	Patients Excluded (*n*)[a]	Did Not Progress			Progressed			Adjusted HR (95% CI)[b]	*p* value
		Patients (*n*)	Deaths after landmark time (*n*)	Median OS (yr)	Patients (*n*)	Deaths after landmark time (*n*)	Median OS (yr)		
6	6	338	148	7.6	96	61	3.5	1.77 (1.28–2.45)	.006
12	22	272	111	7.2	146	85	3.8	1.60 (1.16–2.20)	.0036
18	39	222	77	7.1	179	104	3.7	1.82 (1.28–2.58)	.009
24	74	186	65	6.8	180	93	4.1	1.46 (0.99–2.14)	.06

[a]Reasons for exclusion: (a) death before landmark time ($n = 6$ [6 months], $n = 19$ [12 months], $n = 34$ [18 months], $n = 57$ [24 months]); (b) follow-up not reaching landmark time ($n = 3$ [12 months], $n = 5$ [18 month], $n = 17$ [24 months]).
[b]HR for death in patients with disease progression at the specified landmark time compared with those without disease progression. Adjusted for age, gender, tumor grade and tumor origin, chromogranin A level, and postprogression treatments.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

tumors. Approximately half of the cohort had functional tumors, as defined by the presence of symptoms of hormone hypersecretion; of patients who had functional tumors, 65% had small bowel NET, 24% had other NET (of which 82% were unknown primary), and 11% had panNET. Approximately half of the patient cohort had baseline elevations in the biomarker CgA (defined as above twice the upper limit of normal). Patients initiated treatment between 1995 and 2013; 12% started treatment before 2003. Patients initiated treatment with SSA a median of 3.9 months after being diagnosed with metastatic disease. The median follow-up time for these patients, measured from time of initiation of treatment with SSA was 7.1 years. More than 90% of patients received some form of additional therapy after progression.

During the follow-up period, there were a total of 311 progression events, based on medical record review. These included 147 patients (47%) who were classified as having progressed on the basis of review of radiologic reports, 137 (44%) patients who were classified as having progressed on the basis of initiating of a subsequent treatment, 3 patients who experienced (10%) clinical progression as documented in the chart, and 24 (6%) who had died. The median PFS was 17 months (95% confidence limits [CL], 14, 22 months). There were 215 deaths from the initiation of SSA treatment to the end of the study period. The median OS was 6.4 years (95% CL, 5.9, 8.0 years) (Table 1). We additionally evaluated potential prognostic factors for both PFS and OS in our cohort by using multivariate analyses. We found that male gender, tumor origin outside of the small bowel or pancreas, poorly

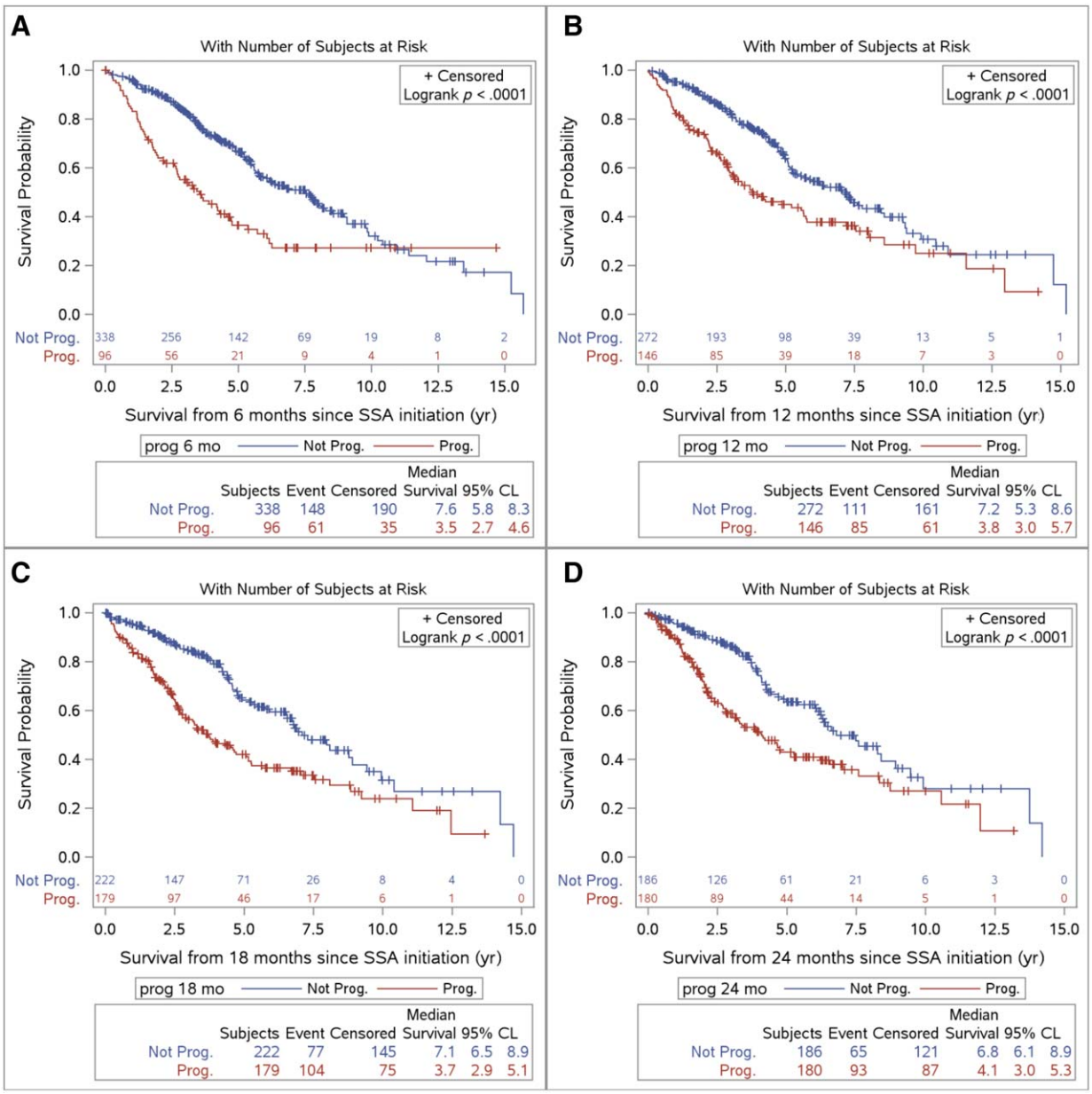

Figure 1. Kaplan-Meier curves demonstrating overall survival for patients receiving treatment with single-agent SSAs who progressed or did not progress at each landmark time. **(A)**: 6 months. **(B)**: 12 months. **(C)**: 18 months. **(D)**: 24 months.

Abbreviations: CL, confidence limits; Prog., progressed; SSA, somatostatin analog.

differentiated histologic features, and elevated CgA were associated with shorter PFS. Older age, poorly differentiated histologic features, and elevated CGA were associated with shorter OS.

Association Between Disease Progression Endpoints and Overall Survival in Patients Receiving Treatment with SSAs

To assess associations between progression-free and overall survival, we used a Kendall tau correlation and bootstrap validation. As noted previously, the median PFS for the entire patient cohort was 17 months and the median OS was 6.4 years. The calculated Kendall tau correlation between PFS and OS was 0.31 (bootstrap SEM, 0.03; 95% confidence interval [CI], 0.25–0.37; $p < .0001$), suggesting a statistically significant association between PFS and OS in our cohort.

A limitation of using a Kendall tau correlation to assess associations between PFS and OS is that it does not take into account an inherent association between PFS and OS because deaths included in the assessment of PFS are also included in the OS analysis. A landmark analysis, in contrast, evaluates associations between disease progression and overall survival and eliminates from the analysis patients who die before progression, avoiding this potential confounding effect. We therefore also used a landmark analysis to assess associations between disease progression and OS, evaluating differences in survival between those who progressed and those who did not progress at landmark times of 6, 12, 18, and 24 months from initiation of SSA treatment. The adjusted HRs (aHRs) for death were 1.77, 1.60, and 1.82 for patients whose disease had progressed at 6, 12, and 18 months, respectively, compared with those whose disease had not progressed ($p < .05$ for all comparisons; Table 2).

Table 3. Progression-free and overall survival in patients receiving everolimus

Variable	PFS			OS		
	Events (progression + deaths[a])/ at risk (*n/n*)	Median PFS (95% CL), yr	*p* value[b]	Events (deaths)/ at risk (*n/n*)	Median OS (95% CL), yr	*p* value[c]
Entire cohort	95/109	0.8 (0.6, 1.1)		62/109	3.1 (2.1, 4.1)	
Age						
≥55 yr	31/38	0.8 (0.6, 1.1)	.44	20/38	3.1 (1.5, NE)	.92
<55 yr	64/71	0.8 (0.6, 1.3)		42/71	3.3 (2.1, 4.3)	
Gender						
Male	54/61	0.8 (0.6, 1.1)	.75	36/61	3.0 (1.8, 4.3)	.85
Female	41/48	0.8 (0.6, 1.3)		26/48	3.4 (1.7, 4.4)	
Tumor origin						
Small bowel	23/27	0.9 (0.7, 1.7)		17/27	2.1 (1.4, NE)	
Pancreas	47/55	0.9 (0.6, 1.4)	.90	29/55	4.1 (1.9, 5.2)	.45
Other	25/27	0.6 (0.4, 0.9)	.09	16/27	3.0 (1.6, 4.0)	.82
Tumor histology						
Well differentiated	92/106	0.8 (0.6, 1.1)	.15	60/106	3.1 (1.9, 4.3)	.76
Poorly differentiated	3/3	0.3 (0.3, 1.0)		2/3	2.8 (2.5, NE)	
Functional status						
Functional	27/31	0.8 (0.7, 1.4)	.93	19/31	3.1 (1.4, NE)	.72
Nonfunctional	68/78	0.8 (0.6, 1.1)		43/78	3.3 (2.4, 4.3)	
Baseline CgA						
<2 times ULN	42/48	0.9 (0.6, 1.4)		21/48	4.1 (2.5, NE)	
≥2 times ULN	50/56	0.8 (0.5, 1.1)	.41	37/56	2.8 (1.6, 3.8)	.15
Missing	3/5	0.8 (0.4, 1.1)	.62	4/5	1.3 (0.5, 4.0)	.26

[a]66 (70%) radiological progression, 19 (20%) next treatment, 6 (6%) clinical progression, and 4 (4%) deaths without any progression.
[b]Calculated with a Cox model adjusted for age, gender, tumor differentiation and tumor origin, CgA level, and functional status.
[c]Calculated with Cox model adjusted for age, gender, tumor differentiation and tumor origin, CgA level, functional status, and postprogression treatments.
Abbreviations: CgA, chromogranin A; CL, confidence limits; NE, not estimable; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

Table 4. Landmark analysis of associations between progressive disease and overall survival at 3, 6, 12, and 18 months (overall cohort) in patients receiving treatment with everolimus ($n = 109$)

Landmark time (mo)	Patients excluded (*n*)	Did not progress			Progressed			Adjusted HR (95% CI)[a]	*p* value
		Patients (*n*)	Deaths after landmark time (*n*)	Median OS (yr)	Patients (*n*)	Deaths after landmark time (*n*)	Median OS (yr)		
3	2	95	50	3.5	12	10	1.0	2.62 (1.22–5.62)	.01
6	9	77	35	3.6	23	18	1.0	2.33 (1.18–4.61)	.02
12	20	48	17	NE	28	41	1.6	2.82 (1.30–6.12)	.001
18	57	8	0	NE	44	26	1.6	NE	NE

[a]HR for death in patients with disease progression at the specified landmark time compared with those without disease progression. Adjusted for age, gender, tumor grade and tumor origin, chromogranin A level, and postprogression treatments.
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

At 24 months, the aHR was 1.46 ($p = .06$). Kaplan-Meier analyses also showed strong associations between progression and survival at all landmark times (Fig. 1). For example, the median OS for patients who progressed at 6 months was 3.5 years compared with 7.6 years for those who did not progress ($p = .0006$). At other landmark times, the median OS ranged from 3.7 to 4.1 years for patients who progressed on SSA and from 6.8 to 7.2 years for those who did not.

We additionally explored whether associations between disease progression on SSAs and survival differed in patient subgroups. By using 6-month landmark intervals, we evaluated potential differences in associations based on site of tumor origin (supplemental online Table 1), baseline CgA level (supplemental online Table 2), and functional status (supplemental online Table 3). The association between disease progression on SSA and OS appeared to be somewhat stronger in pancreatic NET, in patients with baseline elevations in CgA, and in patients with functional tumors. However, in most comparisons, these differences were not statistically significant when we performed formal testing for interactions. We did not observe significant differences in progression/OS associations based on age or gender.

Associations Between Disease Progression Endpoints and Overall Survival in Patients Receiving Treatment with Everolimus

To explore whether we would find similar associations between disease progression endpoints and treatment with other agents, we identified 109 patients in our database who had received treatment with the mTOR inhibitor everolimus. Within this cohort, the median age was 55 years; 56 patients were male, 97% had well differentiated tumors, 25% had neuroendocrine tumors of the small intestine, 50% had neuroendocrine tumors of the

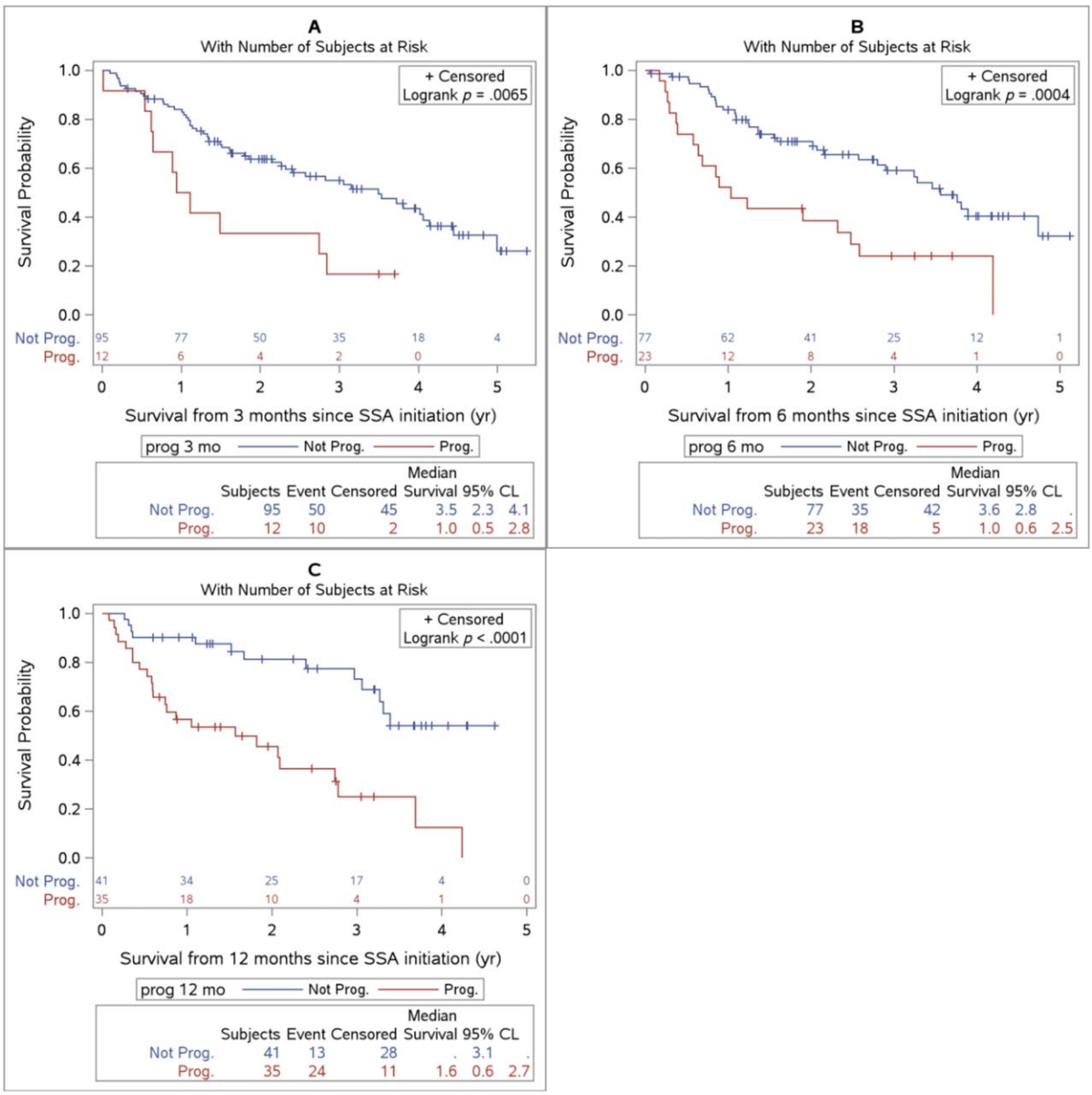

Figure 2. Kaplan Meier Curves demonstrating overall survival for patients receiving everolimus who did or did not progress at landmark time. **(A)**: 3 months. **(B)**: 6 months. **(C)**: 12 months.

Abbreviations: CL, confidence limits; Prog., progressed; SSA, somatostatin analog.

pancreas, and 25% had neuroendocrine tumors of other sites. With a median follow-up time of 3.25 years, there were 66 progression events and 62 deaths. The median PFS for patients receiving everolimus was 0.8 years (9.6 months), and the median OS was 3.1 years (Table 3). The calculated Kendall tau correlation between PFS and OS was 0.44 (bootstrap SEM, 0.05; 95% CI, 0.33–0.54; $p < .0001$), suggesting that, as observed in patients treated with somatostatin analogs, there was a statistically significant association between PFS and OS. Using a landmark analysis, we found that for patients receiving everolimus the aHRs for death were 2.62, 2.33, and 2.82 for patients whose disease had progressed at 3, 6, and 12 months compared with those whose disease had not ($p \leq .01$ for all comparisons; Table 4 and Fig. 2). Given the relatively small sample size, we did not perform subgroup analyses in this cohort.

Discussion

According to recent, randomized trials, somatostatin analogs are increasingly used as a first-line therapy for patients with advanced neuroendocrine tumors [14]. These trials, however, used time to tumor progression or PFS as primary endpoints to demonstrate efficacy, and the extent to which the improvements in disease progression endpoints with somatostatin analogs may translate into improved OS is not known. Our study provides evidence for an association between disease progression endpoints and overall survival in a large, observational cohort of neuroendocrine tumor patients receiving treatment with single-agent somatostatin analogs.

OS has historically been the standard endpoint for assessing the benefit of therapeutic interventions in a broad range of malignancies, although is not always a practical or feasible

endpoint in clinical trials. PFS has therefore been used as a surrogate endpoint, and in clinical trials of cytotoxic chemotherapy in advanced colorectal cancer, for example, PFS correlated well with OS [7, 17]. In recent years, however, direct associations between PFS and OS have been more difficult to demonstrate. Reasons for this include relatively long postprogression survival durations and the likelihood that patients who progress will receive additional lines of treatment after progression, including crossover to an active treatment arm in clinical trials [18, 19]. In some settings, an association between PFS and OS has nevertheless still been evident: In a meta-analysis of 1,158 patients with renal cell carcinoma receiving molecularly targeted therapies, for example, PFS was clearly associated with OS [20]. In other settings, however, a clear association between PFS and overall survival has not been clearly established. In a large analysis of more than 16,000 patients with metastatic colorectal cancer, many of whom had received newer biologic agents, only a modest correlation between PFS and OS was observed [21]. An FDA-sponsored meta-analysis of more than 12,000 patients receiving therapy in randomized clinical trials for lung cancer performed between 2003 and 2014 found no clear association between PFS and OS [22]. Associations between PFS and OS in recent trials of patients with advanced breast cancer or ovarian cancer have also been inconsistent [10, 23].

Concerns about long survival durations and postprogression therapy precluding demonstration of potential associations between progression endpoints and OS are particularly relevant in NETs, which often pursue a more indolent course than other malignancies and in which OS durations may extend to several years. Interestingly, however, a recent study, which evaluated associations between disease progression endpoints and OS in patients with NETs, did in fact demonstrate an association between median time to tumor progression and median OS [24]. This analysis included a range of studies and included data from 22 trials comprising more than 2,500 patients. A potential limitation of this study, however, is that the analysis was based on overall trial results rather than analysis of individual patient data. The current study, in contrast, is based on analysis of patient-level data.

Additionally, the prior study evaluated both large, randomized studies and single-arm studies of novel therapies, many of which had been performed in a late-stage, treatment-refractory setting. The inclusion of late-stage studies may have reduced the influence of postprogression therapy on the PFS/OS association in this cohort. The median OS of 2.5 years reported in this study is in fact similar to the median OS of 3.1 years (from time of treatment initiation) observed in the cohort of patients in our study receiving everolimus, in whom we also observed an association between progression endpoints and OS and who presumably had relatively late-stage disease.

The median OS of 6.4 years observed in our cohort of patients receiving somatostatin analogs, on the other hand, is more consistent with overall survival durations of patients with advanced NET measured from time of diagnosis of metastatic disease [1, 2]. Patients in our study initiated SSA early in the course of their metastatic disease, a median of 3 months after their diagnosis of metastatic disease, and experienced a median progression-free survival of 1.5 years. Overall survival (6.4 years), measured from time of initiation of SSA, was more than 4 times longer than PFS. Additionally, over 90% of patients in our study received some form of therapy after disease progression. Despite the relatively long postprogression survival duration and the common use of postprogression therapy in this cohort, we observed a clear association between progression endpoints and OS. A clear association between PFS and OS was observed by using the Kendall tau test, and associations between progression status and survival were observed by using a landmark analysis. Somewhat stronger associations were observed in pancreatic NET, patients with elevated CGA, and functional tumors. However, these differences did not reach statistical significance in most analyses. It is possible that the stronger associations between PFS and OS in these subgroups were observed because these subgroups tended to also have shorter survival and therefore less potential for confounding due to postprogression therapy.

The association between PFS and OS observed in our study supports the continued use of PFS as a clinically meaningful endpoint in NET trials, as was originally recommended at a NET Clinical Trials Planning Meeting sponsored by the National Cancer Institute. Our study nevertheless has several limitations. The retrospective nature of this study made precise measurement of PFS challenging; tumor progression was measured by using a composite definition that incorporated not only radiologic progression but also clinical progression and initiation of subsequent therapies, which could have overestimated the number of true progression events. Additionally, we cannot differentiate the potential role of tumor biology versus treatment effect: absent a nontreatment comparator arm in this observational study, we are not able to draw any direct or specific conclusions about the treatment effect of somatostatin analogs or everolimus in this setting [25, 26].

Conclusion

Despite the preceding limitations, by inference our results can be taken to further support the use of SSAs and other therapies associated with a PFS benefit in patients advanced NET. We found that tumor progression endpoints were associated with overall survival in a large, single-institution cohort of patients with advanced neuroendocrine tumors treated with somatostatin analogs and in a second cohort of patients treated with everolimus. The observation of an association between tumor progression and survival in a cohort of neuroendocrine tumor patients treated with somatostatin analogs early in the course of their metastatic disease, nearly all of whom received some form of postprogression treatment, is particularly intriguing. Definitive evidence that specific treatments shown to improve PFS will also improve OS in neuroendocrine tumors, however, will require future analysis of data from large, prospective studies.

Acknowledgments

We are grateful for support from the Gitta and Saul Kurlat Fund for Neuroendocrine Tumor Research, Jane Dybowski Fund for Neuroendocrine Cancer, McIntyre Family Fund for Neuroendocrine Tumor Research, Lipson Family Fund, Goldhirsh-Yellin Foundation Fund for Neuroendocrine Tumor Research, the Murphy Family Fund for Carcinoid Tumor Research, and the Caring for Carcinoid Foundation. This study was funded in part with a grant from Ipsen Pharmaceuticals. This work was also supported by U.S. National Institutes of Health Grant R01 CA151532 to M.H.K. The abstract was submitted for presentation and accepted for

publication at the 2015 American Society of Clinical Oncology annual meeting in Chicago, Illinois.

Author Contributions

Conception/Design: Monica Ter-Minassian, Sui Zhang, Nichole V. Brooks, Lauren K. Brais, Jennifer A. Chan, David C. Christiani, Xihong Lin, Sylvie Gabriel, Jérôme Dinet, Matthew H. Kulke

Provision of study material or patients: Monica Ter-Minassian, Sui Zhang, Nichole V. Brooks, Lauren K. Brais, Jennifer A. Chan, David C. Christiani, Xihong Lin, Sylvie Gabriel, Jérôme Dinet, Matthew H. Kulke

Collection and/or assembly of data: Monica Ter-Minassian, Sui Zhang, Nichole V. Brooks, Lauren K. Brais, Jennifer A. Chan, David C. Christiani, Xihong Lin, Sylvie Gabriel, Jérôme Dinet, Matthew H. Kulke

Data analysis and interpretation: Monica Ter-Minassian, Sui Zhang, Nichole V. Brooks, Lauren K. Brais, Jennifer A. Chan, David C. Christiani, Xihong Lin, Sylvie Gabriel, Jérôme Dinet, Matthew H. Kulke

Manuscript writing: Monica Ter-Minassian, Sui Zhang, Nichole V. Brooks, Lauren K. Brais, Jennifer A. Chan, David C. Christiani, Xihong Lin, Sylvie Gabriel, Jérôme Dinet, Matthew H. Kulke

Final approval of manuscript: Monica Ter-Minassian, Sui Zhang, Nichole V. Brooks, Lauren K. Brais, Jennifer A. Chan, David C. Christiani, Xihong Lin, Sylvie Gabriel, Jérôme Dinet, Matthew H. Kulke

Disclosures

Matthew H. Kulke: Ipsen, Novartis (C/A); **Monica Ter-Minassian**: Ipsen Pharmaceuticals (RF); **Jennifer A. Chan**: Ipsen, Lexicon, Novartis (C/A), Eli Lilly, Sanofi-Aventis (RF); **Sylvie Gabriel**: Ipsen Pharma (E); **Jerome Dinet**: Ipsen Pharma (E). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Yao JC, Hassan M, Phan A et al. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–3072.

2. Ter-Minassian M, Chan JA, Hooshmand SM et al. Clinical presentation, recurrence, and survival in patients with neuroendocrine tumors: Results from a prospective institutional database. Endocr Relat Cancer 2013;20:187–196.

3. Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014;371:1556–1557.

4. Yao JC, Shah MH, Ito T et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514–523.

5. Raymond E, Dahan L, Raoul JL et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501–513.

6. Pavel ME, Hainsworth JD, Baudin E et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): A randomised, placebo-controlled, phase 3 study. Lancet 2011;378:2005–2012.

7. Buyse M, Burzykowski T, Carroll K et al. Progression-free survival is a surrogate for survival in advanced colorectal cancer. J Clin Oncol 2007;25:5218–5224.

8. Yao JC, Fazio N, Singh S et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): A randomised, placebo-controlled, phase 3 study. Lancet 2016;387:968–977.

9. Kulke MH, Siu LL, Tepper JE et al. Future directions in the treatment of neuroendocrine tumors: Consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol 2011;29:934–943.

10. Adunlin G, Cyrus JW, Dranitsaris G. Correlation between progression-free survival and overall survival in metastatic breast cancer patients receiving anthracyclines, taxanes, or targeted therapies: A trial-level meta-analysis. Breast Cancer Res Treat 2015;154:591–608.

11. Strosberg J, Wolin E, Chasen B et al. NETTER-1 phase III: Progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-Lu-Dotatate [abstract]. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2016 Annual Conference; San Francisco, CA. J Clin Oncol 2016;34(suppl 4S):Abstract 194.

12. Rinke A, Muller HH, Schade-Brittinger C et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group. J Clin Oncol 2009;27:4656–4663.

13. Rinke A, Wittenberg M, Schade-Brittinger C et al. Placebo controlled, double blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): Results on long term survival. Neuroendocrinology 2017;104:26–32.

14. Kulke MH, Shah MH, Benson AB 3rd et al. Neuroendocrine tumors, version 1.2015. J Natl Compr Canc Netw 2015;13:78–108.

15. Akristas MG, Siebert J. A test for partial correlation with censored astronomical data. Mon Not R Astron Soc 1995;278:919–924.

16. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983;1:710–719.

17. Tang PA, Bentzen SM, Chen EX et al. Surrogate end points for median overall survival in metastatic colorectal cancer: Literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. J Clin Oncol 2007;25:4562–4568.

18. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 2009;101:1642–1649.

19. Venook AP, Tabernero J. Progression-free survival: Helpful biomarker or clinically meaningless end point? J Clin Oncol 2015;33:4–6.

20. Heng DY, Xie W, Bjarnason GA et al. Progression-free survival as a predictor of overall survival in metastatic renal cell carcinoma treated with contemporary targeted therapy. Cancer 2011;117:2637–2642.

21. Shi Q, de Gramont A, Grothey A et al. Individual patient data analysis of progression-free survival versus overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: Findings from the analysis and research in cancers of the digestive system database. J Clin Oncol 2015;33:22–28.

22. Blumenthal GM, Karuri SW, Zhang H et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. J Clin Oncol 2015;33:1008–1014.

23. Shimokawa M, Ohki M, Kaku T. Correlation of progression-free and post-progression survival with overall survival in phase III trials of first-line chemotherapy for advanced epithelial ovarian cancer. Eur J Gynaecol Oncol 2015;36:370–375.

24. Singh S, Wang X, Law C. Association between time to disease progression end points and overall survival in patients with neuroendocrine tumors. Gastrointest Cancer Targets Ther 2014;2014:103–113.

25. Prentice RL. Surrogate endpoints in clinical trials: Definition and operational criteria. Stat Med 1989;8:431–440.

26. Hughes MD. Practical issues arising in an exploratory analysis evaluating progression-free survival as a surrogate endpoint for overall survival in advanced colorectal cancer. Stat Methods Med Res 2008;17:487–495.

See http://www.TheOncologist.com for supplemental material available online.